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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/576,633 | 11/14/2006 | Shite Sebastian | 14964 | 4672 |

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ROBERTS MLOTKOWSKI SAFRAN & COLE, P.C.
Intellectual Property Department
P.O. Box 10064
MCLEAN, VA 22102-8064

| EXAMINER | |
|---|---|
| OGUNBIYI, OLUWATOSIN A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 04/07/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

lgallaugher@rmsclaw.com
dbeltran@rmsclaw.com
bdiaz@rmsclaw.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/576,633 | SEBASTIAN ET AL. | |
| | Examiner | Art Unit | |
| | OLUWATOSIN OGUNBIYI | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

The amendment filed 1/7/09 has been entered into the record. Claims 1-12 are pending and are under examination.

## *Rejections Withdrawn*

The rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims.

## *Rejection Maintained.*

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for the reasons set forth in previous action mailed 10/7/08 and as set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for detecting the presence or absence of a bacterium in a sample selected from a wound, a body fluid, or fluid from a wound, said method

comprising the steps of: a) contacting said sample with a detectably labeled synthetic alpha-1-proteinase inhibitor reactive site loop domain peptide substrate under conditions that result in cleavage of said substrate by an enzyme produced in said sample by a bacterium; and b) detecting a cleavage or an absence of cleavage of the substrate, the cleavage of the substrate indicating the presence of the bacterium in the sample and absence of the cleavage of the substrate indicating absence of the bacterium in the sample.

The breadth of claims covers the detection of any bacterium in a wound, a body fluid, or fluid from a wound via the cleavage of synthetic alpha-1-proteinase inhibitor reactive site loop domain peptide substrate by any enzyme produced by said bacterium.

The specification contemplates the detection of the presence or absence of bacteria in a wound surfaces and body fluids (see p. 11 last bridging paragraph to p.12 lines 1-10). However, the instantly claimed method does not take into account that wound surfaces and body fluids comprise proteases (Steffensen et al Crit Rev Oral Biol Med 12(5):373-398, 2001, Armstrong et al J Am Podiatr Med Assoc 92(1): 12-18, 1998 and Ungar et al J Exp Med. 1961 January 31; 113(2): 359–380) that may be confounding factors in the instant method of bacterium detection. The specification in fig. 1A teaches that metalloproteinases (MMP1, MMP8 etc) from bacteria such as *S. aureus* cleave the RSL peptide of alpha-1-proteinase inhibitor. However, host matrix metalloproteinases such as MMP8 play a role in wound healing and can be found in wound tissue. Even bacterial infection of a wound results in prolonged elevation of proinflammatory cytokines which in turn causes increases in levels of matrix metalloproteinases released from neutrophils and macrophages Cullen et al WO 03/040406 A2, 2003, p. 1 lines 24-28, p. 3 lines 8-15). The instant method as claimed does not control for cleavage of the RSL domain peptide by

non-bacterial enzymes or proteases that may be present in wound surfaces and body fluids because the same type of bacterial enzymes that cleave RSL domain of alpha-1-proteinase inhibitor is present in wound surface. For example, since host matrix metalloproteinases e.g. MMP8, MMP1 are present in wound tissue and detection of cleavage of RSL by these host enzymes will not correctly indicate that bacteria is present in said wounds. Desrochers et al (J. Clin. Invest. 1991 88:2258-2265, see whole document especially fig.5) teaches that human MMP1 cleaves the RSL domain of alpha-1-proteinase inhibitor. The instantly claimed method does not distinguish between modification of RSL domain peptides by proteases produced bacteria and by host proteases present in wound surfaces and body fluids.

Example 2 p. 18-19, in the specification teaches that wound dressings obtained from patients (no information on the wounds or patients was obtained) were extracted in PBS overnight and cleavage reaction was carried out on these samples with an RSL domain peptide of alpha-1-proteinase inhibitor. Figures 10A-D present the results from this assay and the figure legend states that the graphs illustrate the relative fluorescence of bacteria extracted from wound dressings. Since wound surfaces contain host enzymes that can cleave the detectably labeled RSL domain peptide it is not certain that the fluorescence observed is due to enzymes produced by bacteria. No information on the wounds or patients was obtained and the samples were not cultured to determine that they were infected with bacteria. In view of the above considerations undue experimentation would be required of the skilled artisan to practice the invention as claimed. Desrochers teaches that matrix metalloproteinase 1 (MMP1) is synthesized in epithelial cells which can be found in wounds in response to proinflammatory cytokines (p. 2258 column 2) which in turn can be induced by the presence of bacteria (See. Xue et al Clinical and

Experimental Ophthalmology vol. 28 issue 3 p. 197-200, 12/25/01). Thus, the same bacterial enzyme e.g. MMP1 that can be produced by bacteria that cleaves RSL domain of alpha-1-proteinase inhibitor (see drawings fig. 1A) is also produced i.e. MMP1 by the body in response to bacterial infection.

Applicants' arguments:

It is submitted that the specification clearly demonstrates that enzymes which are produced/secreted by a broad range of pathogenic bacteria can be detected by the method as now claimed herein. This in turn can provide an indication of the presence of the producing/secreting bacteria in the wound. In the second place, WO 03/040406 indicates at Page 1, lines 24-28 that it is the persistent presence of bacteria in a wound which results in increases in the levels of metalloproteinases. Thus to the extent that metalloproteinases present in the wound sample via this mechanism can be detected by the presently claimed method, the method of this invention still provides a useful way for detecting the presence or absence of pathogenic microorganisms.

Applicants' arguments have been carefully considered but have not been found persuasive. Although, some bacteria produce enzymes that cleave alpha-1-proteinase RSL , the specification does not correlate the cleavage of alpha-1-proteinase by extracts from wound dressings with the presence of bacteria (see example 2). Example 2 p. 18-19, in the specification teaches that wound dressings obtained from patients (no information on the wounds or patients was obtained) were extracted in PBS overnight and cleavage reaction was carried out on these samples with an RSL domain peptide of alpha-1-proteinase inhibitor RSL . Figures 10A-D present the results from this assay and the figure legend states that the graphs illustrate the relative fluorescence of bacteria extracted from wound dressings. It is not clear how figure 10A-D depicts relative fluorescence of bacteria since the detection signal is on the RSL domain peptide substrate and not on the bacteria (p. 12 lines 11-32). Furthermore, no information on the wounds or patients was obtained and it is not known whether the dressings were from chronic

wounds, whether the wounds were infected with bacteria. Based on the teachings in the art that wounds contain enzymes (see above) which can also cleave alpha-1-proteinase inhibitor RSL, there is no control for this in example 2 and there is no information to confirm that the wounds from which the wound dressings were obtained were ever infected with bacteria. There is a confounding factor i.e. the presence in wounds, wound fluids and body fluids of enzymes that also cleave alpha-1-proteinase inhibitor RSL. The wound dressing extracts were not cultured to determine that they contained bacteria. Since wounds including chronic wounds, body fluids contain host enzymes that can cleave the detectably labeled RSL domain peptide it is not certain that the fluorescence observed is due to enzymes produced by bacteria. Desrochers et al teaches that matrix metalloproteinase 1 (MMP1) is synthesized in epithelial cells which can be found in wounds in response to proinflammatory cytokines (p. 2258 column 2) and proinflammatory cytokines can be induced by the presence of bacteria (See. Xue et al Clinical and Experimental Ophthalmology vol. 28 issue 3 p. 197-200, 12/25/01. See p. 197 column 2 first paragraph before "methods".). Thus, the same bacterial enzyme e.g. MMP1 that can be produced by bacteria that cleaves RSL domain of alpha-1-proteinase inhibitor (see drawings fig. 1A) is also produced i.e. MMP1 by the body in response to bacterial infection. The concept of enzymatic cleavage of substrates by bacterial enzymes by bacteria for detection of said bacteria in human body fluids is known in the art (See Yolken et al. Clin. Chem. 27/9, 1490-1498, cited in IDS). Yolken et al teach (see abstract) that this technique is based on the fact that bacteria possesses enzymes that are not produced by mammalian cells and that detection of these enzymes in a body fluid would be indicative of microbial infection. Yolken et al teach that the enzymatic activity be appropriately identified as being of microbial origin. The examples in the specification e.g.

example 1 and example 10 detected cleavage of RSL domain of alpha-1-proteinase inhibitor by contacting samples of wound extracts from dressing or clinical swabs of wound with labeled RSL domain of alpha-1-proteinase inhibitor *but does not correlate said cleavage with the presence of bacteria in said wound -no information on the wound dressing or the patients was known* i.e. whether the wounds were infected with bacteria or not and because of confounding factors i.e. the presence of human enzymes that produce enzymes that also cleave RSL domain of alpha-1-proteinase inhibitor, undue experimentation would be required by the skilled artisan to use the method as claimed to detect the presence or absence of a bacterium in a wound or wound fluid or body fluid (including wound fluid).

**Status of Claims**

Claims 1-12 are rejected. No claims allowed.

**Conclusion**

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to OLUWATOSIN OGUNBIYI whose telephone number is 571-272-9939. The examiner can normally be reached on M-F 8:30 am- 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645